

FOOD AND DRUG *Research* LABORATORIES, INC. #2



MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378

FINAL

August 11, 1972

Teratologic Evaluation of FDA 71-15

(Gum Arabic)

in

Mice, Rats, Hamsters and Rabbits

Final report-Teratologic Evaluation of FDA 71-15 (Gum Arabic) in Mice, Rats,
Hamsters & Rabbits
8/11/72

M I C E

Food and Drug Research Laboratories

I N C O R P O R A T E D



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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 11, 1972

Laboratory No. 0893 e
Contract No. FDA 71-260

Sample: Fine white powdered material.

Marking: FDA 71-15 (Gum arabic)

Examination Requested: Teratologic evaluation of FDA 71-15 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 1600 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs: each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge, Ph. D.

Vice President

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor of any members of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 71 & 72; 77 through 80

Date June 30, 1972

Material: FDA 71-15

Laboratory No. 0893 e

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
71	Sham	0	23	20	23	20
72	Aspirin*	150	24	21	24	21
77	FDA 71-15	16	22	20	22	20
78	FDA 71-15	75	22	22	21	21
79	FDA 71-15	350	23	19	23	19
80	FDA 71-15	1600	31	20	30	20

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 71 & 72; 77 through 80

Date: June 30, 1972

Material: FDA 71-15

Reproduction Data
(Mice)

Laboratory No.: 0893 e

Table 2

Group:	71	72	77	78	79	80
Dose (mg/kg):	Sham	Aspirin**	16	75	350	1600
Pregnancies						
Total No.	20	21	20	22	19	20
Died or Aborted (before Day 17)	0	1	0	1	0	1
To term (on Day 17)	20	21	20	21	19	20
Corpora Lutea						
Total No.						
Average/dam mated						
Live Litters						
Total No.*	20	21	20	21	19	20
Implant Sites						
Total No.	247	265	260	270	235	252
Average/dam*	12.4	12.6	13.0	12.9	12.4	12.6
Resorptions						
Total No.*	8	10	17	12	13	13
Dams with 1 or more sites resorbed	7	8	10	8	5	10
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	35.0	38.1	50.0	38.1	26.3	50.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	237	255	242	255	221	237
Average/dam*	11.9	12.1	12.1	12.1	11.6	11.9
Sex ratio (M/F)	1.0	0.82	0.78	0.90	1.15	1.03
Dead Fetuses						
Total No.*	2	0	4	3	1	2
Dams with 1 or more dead	2	--	3	3	1	2
Dams with all dead	0	--	0	0	0	0
Per cent partial dead	10.0	--	15.0	14.3	5.26	10.0
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.96	0.87	0.95	0.95	0.98	0.88

*Includes only those dams examined at term.

Groups 71 and 72; 77 through 80

Laboratory No. 0893 e

Table 3

Material FDA 71-15

Date June 30, 1972

Summary of Skeletal Findings
(Mice)

Findings	Group No. Dose (mg/kg)	71 Sham	72 Aspirin**	77 16	78 75	79 350	80 1600
Live Fetuses Examined (at term)		164/20	179/21	166/20	177/21	152/19	162/20
Sternebrae							
Incomplete oss.		52/17	79/18	51/16	20/9	33/10	46/16
Scrambled							
Bipartite		6/4	4/3			2/2	1/1
Fused							
Extra		2/1	1/1			2/2	
Missing		11/7	19/6	7/4	5/4	3/3	30/7
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		20/7	16/9	25/13		23/11	7/2
Other							
Vertebrae							
Incomplete oss.				1/1			6/1
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis		1/1	1/1	1/1			
Tail defects							
Other							
Skull							
Incomplete closure			6/2				
Missing							
Craniosinosis							
Other							
Extremities							
Incomplete oss.							7/2
Missing							
Extra							
Miscellaneous							
Hyoid; missing		25/11	43/13	33/9	44/13	17/9	54/16
Hyoid; reduced		10/7	11/6	7/5	12/10	10/7	7/6

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Material FDA 71-15

Laboratory No. 0893 e

Table 3-a

Summary of Soft Tissue Abnormalities
(Mice)

Group	Material	Dose level mg/kg	Dam	Pup	Description
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None Observed

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Table 4

Species Mice

Laboratory No. 0893

Average Body Weights*

Group	Material	Dose Level	Day				
			0	6	11	15	
71	Sham	0.0	31.2	34.1	36.6	46.6	53.5 (20)
72	Aspirin**	150.0	31.8	33.8	36.2	44.1	49.9 (21)
77	FDA 71-15	16.0	30.5	32.4	37.4	46.3	52.9 (20)
78	FDA 71-15	75.0	30.0	33.7	37.5	46.0	53.1 (21)
79	FDA 71-15	350.0	32.5	34.6	38.2	47.2	53.7 (19)
80	FDA 71-15	1600.0	39.7	33.5	34.9	42.9	49.6 (20)

* Of pregnant dams
 ** Number of surviving dams in parentheses (c.f. Table I)
 *** Positive control:



Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

Group 71 Date June 30, 1972

Appendix II

Material Sham Laboratory No. 0893

Reproduction Data in Mice (Individual)

Dose 0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
S 3211	P		9	9		5	4	1.13	
S 3212	P		9	9		3	6	1.01	
S 3213	P		15	15		6	9	0.98	
S 3214	P		11	11		4	7	1.07	
S 3215	P		13	13		5	8	1.03	
S 3216	P		11	11		4	7	1.00	
S 3217	P		12	10		4	6	0.98	
S 3218	P		16	16		11	5	1.00	
S 3219	P		8	8		4	4	0.86	
S 3220	P		12	12		6	6	0.91	
S 3221	P		19	18	1	12	6	0.84	
S 3222	P		14	13		7	6	0.92	1
S 3223	P		17	16		12	4	0.91	1
S 3224	NP		0					--	
S 3225	NP		0					--	
S 3226	P		14	13		9	4	0.89	1
S 3227	NP		0					--	
S 3228	P		13	11	1	5	6	1.05	1
S 3229									
S 3230									
S 3231									
S 3232									
S 3233									
S 3234	P		10	10		4	6	0.75	
S 3235	P		12	12		5	7	0.81	
S 3236	P		11	10		4	6	0.82	1
S 3237	P		9	8		--	--	0.91	1
S 3238	P		12	12		5	7	0.80	

Not assigned
Not assigned
Not assigned
Not assigned
Not assigned

* P = Pregnant; NP = Not Pregnant

Group 72

Appendix II

Date June 30, 1972

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 150 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks	
				Alive	Dead					
A 3211	P		13	12		4	8	1	1.05	
A 3212	NP		0						--	
A 3213	P		14	13		6	7	1	0.91	
A 3214	P		13	12		7	5	1	1.05	
A 3215	NP		0						--	Died Day 12
A 3216	P		14	14		7	7		0.92	
A 3217	P		13	13		8	5		0.96	
A 3218	P		15	15		5	10		0.74	
A 3219	P		15	15		4	11		0.86	
A 3220	P		13	13		8	5		0.73	
A 3221	P		11	9		4	5	2	0.85	
A 3222	P		11	10		1	9	1	0.55	
A 3223	P		11	11		6	5		1.06	
A 3224	P		11	11		5	6		0.84	
A 3225	P		14	14		6	8		0.83	
A 3226	NP		0						--	
A 3227	P		12	11		6	5	1	0.88	
A 3228	P		14	14		9	5		0.93	
A 3229	P		12	12		5	7		0.77	
A 3230	P		10	8		3	5	2	0.83	
A 3231										Not assigned
A 3232	P		14	14		6	8		0.91	
A 3233	P		12	11		5	6	1	0.83	
A 3234	P		11	11		6	5		0.97	
A 3235	P		12	12		4	8		0.77	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 77

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Mice (Individual)

Laboratory No. 0893e

Dose 16 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 3001	P		14	13		9	4	1.29	
E 3002	P		10	6		3	3	0.86	
E 3003	P		15	15		9	6	0.84	
E 3004	P		14	14		5	9	0.87	
E 3005	P		14	12	2	6	8	0.99	
E 3006	NP		0					--	
E 3007	P		11	10		3	7	0.98	
E 3008	P		12	12		4	8	1.02	
E 3009	P		13	12		5	7	0.92	
E 3010	P		11	11		6	5	1.12	
E 3011	P		11	11		5	6	1.01	
E 3012	P		10	9	1	7	2	1.14	
E 3013	P		13	10		5	5	1.01	
E 3014	P		15	12	1	6	7	0.81	
E 3015	P		14	13		5	9	0.94	
E 3016	P		17	16		9	8	1.03	
E 3017	NP		0					--	
E 3018	P		15	15		7	8	0.94	
E 3019	P		14	12		4	8	0.75	
E 3020	P		12	11		2	9	0.97	
E 3021	P		11	11		4	7	0.90	
E 3022	P		14	14		2	12	0.82	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 78

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Mice

(Individual)

Laboratory No. 0893e

Dose 75 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 3031	P		12	12		5	7	0.90	
E 3032	P		14	14		6	8	1.11	
E 3033	P		13	13		5	8	1.04	
E 3034	P		12	11		5	6	0.90	1
E 3035	P		9	9		5	4	1.04	
E 3036	P		14	14		7	7	0.76	
E 3037	P		14	14		7	7	1.03	
E 3038	P		15	15		6	9	0.89	
E 3039	P		9	9		--	--	--	Died Day 9
E 3040	P		10	8	1	3	5	1.04	
E 3041	P		14	13		7	7	0.85	
E 3042	P		14	11		5	6	1.03	
E 3043	P		14	12	1	--	--	0.70	
E 3044	P		11	11		5	6	1.07	
E 3045	P		15	15		8	7	1.01	
E 3046	P		14	13		7	6	0.93	
E 3047	P		13	10		5	5	1.05	
E 3048	P		13	13		6	7	1.09	
E 3049	P		13	12	1	5	7	0.96	
E 3050	P		12	12		5	7	0.61	
E 3051	P		12	12		6	6	1.00	
E 3052	P		12	11		7	4	1.00	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 79

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Mice (Individual)

Laboratory No. 0893e

Dose 350 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 3061	P		10	10		4		1.05	
E 3062	P		13	13		10		0.90	
E 3063	P		12	12		7		0.89	
E 3064	P		9	9		7		1.00	
E 3065	P		16	16		10		1.05	
E 3066	P		13	13		9		0.98	
E 3067	P		15	15		9		0.92	
E 3068	NP		0					--	
E 3069	NP		0					--	
E 3070	P		15	14		7	1	1.08	
E 3071	P		10	10		4		1.04	
E 3072	P		13	13		8		0.88	
E 3073	P		10	9		4	1	1.09	
E 3074	P		4	4		2		1.07	
E 3075	P		10	10		5		1.12	
E 3076	NP		0					--	
E 3077	P		11	8	1	5	2	0.93	
E 3078	P		12	12		6		1.19	
E 3079	NP		0					--	
E 3080	P		15	15		6		1.04	
E 3081	P		18	18		8		0.83	
E 3082	P		14	7		2	7	0.80	
E 3083	P		15	13		5	2	0.85	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 80

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Mice (Individual)

Laboratory No. 0893e

Dose 1600 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 3091	P		14	13	1	M		0.82	
E 3092	P		13	12	1	F		0.91	
E 3093	P		14	12			2	1.14	
E 3094	P		10	10	3	F		0.95	
E 3095	P		16	15	11	F	1	0.95	
E 3096	P		13	13	7	F		0.95	
E 3097	P		15	14	7	F	1	0.96	
E 3098	NP		0						
E 3099	NP		0						
E 3100	NP		0						
E 3101	NP		0						
E 3102	NP		0						
E 3103	NP		0						
E 3104	NP		0						
E 3105	P		13	13	7	F		0.82	
E 3106	P		15	13	7	F	2	0.87	
E 3107	P		12	11	6	F	1	1.00	
E 3108	P		15	15	5	F	10	0.86	
E 3109	P		12	11	5	F	1	1.00	
E 3110	P		13	12	8	F	1	1.00	
E 3111	P		12	12	7	F	5	0.98	
E 3112	NP		0						
E 3113	NP		0						
E 3114	P		13	12	6	F	1	0.83	
E 3115	P		7	6	3	F	1	**	
E 3116	P		11	11	8	F	3	0.83	
E 3117	P		10	10	4	F	6	0.93	

Died Day 14

Continued on next page

* P = Pregnant; NP = Not Pregnant
 ** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 80

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Mice (Individual)

Laboratory No. 0893 e

Dose 1600 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 3118	P	13	13	13	0	3		0.47	
E 3119	NP		0					--	
E 3120	NP		0					--	
E 3121	P	16	11	9	7	2	2	0.59	

* P = Pregnant; NP = Not Pregnant

R A T S

Food and Drug Research Laboratories

I N C O R P O R A T E D



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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 11, 1972

Laboratory No. 0894 e
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-15 (Gum arabic)

Examination Requested: Teratologic evaluation of FDA 71-15 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 1600 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 71 & 72; 77 through 80

Date June 30, 1972

Material: FDA 71-15

Laboratory No. 0894 e

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
71	Snam	0	24	23	24	23
72	Aspirin*	250	24	21	24	21
77	FDA 71-15	16	24	23	24	23
78	FDA 71-15	75	24	22	23	22
79	FDA 71-15	350	24	24	24	24
80	FDA 71-15	1600	24	24	24	24

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 71 & 72; 77 through 80

Date: June 30, 1972

Material: FDA 71-15

Laboratory No.: 0894 e

Table 2
Reproduction Data
(Rats)

Group:	71	72	77	78	79	80
Dose (mg/kg):	Sham	Aspirin**	15	75	350	1600
Pregnancies						
Total No.	23	21	23	23	24	24
Died or Aborted (before Day 20)	0	0	0	1	0	0
To term (on Day 20)	23	21	23	22	24	24
Corpora Lutea						
Total No.	256	257	256	275	284	291
Average/dam mated	10.7	10.7	10.7	11.5	11.8	12.1
Live Litters						
Total No.*	23	19	23	22	24	24
Implant Sites						
Total No.	251	247	245	263	280	284
Average/dam*	10.9	11.8	10.7	12.0	11.7	11.8
Resorptions						
Total No.*	8	59	12	21	6	9
Dams with 1 or more sites resorbed	5	11	5	11	4	5
Dams with all sites resorbed	0	1	0	0	0	0
Per cent partial resorptions	21.7	52.4	21.7	50.0	16.7	20.8
Per cent complete resorptions	--	4.76	--	--	--	--
Live Fetuses						
Total No.	243	184	233	242	274	274
Average/dam*	10.6	8.76	10.1	11.0	11.4	11.4
Sex ratio (M/F)	0.88	1.15	1.04	0.89	0.81	0.67
Dead Fetuses						
Total No.*	0	4	0	0	0	1
Dams with 1 or more dead	--	4	--	--	--	1
Dams with all dead	--	0	--	--	--	0
Per cent partial dead	--	19.0	--	--	--	4.17
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.81	2.36	3.94	3.91	3.98	3.84

*Includes only those dams examined at term.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Laboratory No. 0894 e

Table 3

Material FDA 71-15

Date June 30, 1972

Summary of Skeletal Findings
(Rats)

Findings	Group No.	71	72	77	78	79	80
	Dose (mg/kg)	Sham	Aspirin**	15	75	350	1600
Live Fetuses Examined (at term)		163/23	130/19	158/23	159/22	181/24	184/24
Sternebrae							
Incomplete oss.		14/8	120/19	18/8	9/9	18/11	12/10
Scrambled							
Bipartite			6/5				
Fused							
Extra		1/1					
Missing			71/16	2/2			1/1
Other							
Ribs							
Incomplete oss.			16/9				
Fused/split			19/7				
Wavy		9/4	21/12	3/3	1/1	1/1	7/4
Less than 12			14/4				
More than 13			29/8				
Other							
Vertebrae							
Incomplete oss.		3/3	110/19	2/2	2/2	2/2	
Scrambled							
Fused			11/3				
Extra ctrs. oss.							
Scoliosis			14/3				
Tail defects			2/1				
Other							
Skull							
Incomplete closure		7/5	106/19	9/6	20/12	5/2	9/5
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.			4/4				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		17/9	97/19	14/9	14/9	17/9	11/8
Hyoid; reduced		2/2	2/2	1/1	2/2	2/2	4/2

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Material FDA 71-15

Laboratory No. 0894 e

Table 3-a
Summary of Soft Tissue Abnormalities
(Rats)

Group	Material	Dose level mg/kg	Dam	Pup	Description
72	Aspirin*	250	A 4214	8	Acrania, spina bifida, enterohepatocoele, craniocoele
			A 4218	2	Acrania, spina bifida, craniocoele
			A 4222	1	Acrania, craniocoele
			A 4224	1	Acrania, craniocoele
			A 4229	8	Acrania, craniocoele, spina bifida, hepatocoele

* Positive control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Table 4

Species Rats

Laboratory No. 0894 e

Average Body Weights*

Group	Material	Dose Level	mg/kg	0	6	11	15	20**
71	Sham	0		206	226	248	273	339 (23)
72	Aspirin**	250		205	224	243	260	311 (21)
77	FDA 71-15	16		210	228	248	275	343 (23)
78	FDA 71-15	75		210	227	251	273	344 (22)
79	FDA 71-15	350		216	227	248	273	342 (24)
80	FDA 71-15	1600		200	220	240	264	332 (24)

* Of pregnant dams
 ** Number of surviving dams in parentheses (c.f. Table 1)
 *** Positive control



Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

Date June 30, 1972

Appendix II

Laboratory No. 0894

Group 71

Reproduction Data in Rats (Individual)

Material Sham

Dose 0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
S 4211	P	10	10	10		4	6	4.10	
S 4212	P	12	12	12		6	6	4.10	
S 4213	P	11	11	11		5	6	5.28	
S 4214	P	12	12	12		6	6	3.57	
S 4215	P	8	8	8		4	4	3.57	
S 4216	P	11	9	9		1	8	3.57	
S 4217	P	9	9	7		3	4	3.65	
S 4218	P	14	14	13		5	8	3.58	
S 4219	P	10	10	9		5	4	3.50	
S 4220	P	15	15	15		7	8	3.50	
S 4221	P	10	10	10		4	6	3.72	
S 4222	P	10	10	10		6	4	3.33	
S 4223	P	11	11	11		6	5	4.04	
S 4224	NP	0	0					--	
S 4225	P	12	12	12		7	5	3.84	
S 4226	P	11	7	4		3	1	3.60	
S 4227	P	12	13	12		5	7	4.62	
S 4228	P	9	9	9		7	2	4.07	
S 4229	P	13	13	13		3	10	3.88	
S 4230	P	8	8	8		3	5	3.33	
S 4231	P	12	12	12		6	6	3.44	
S 4232	P	9	9	9		3	6	3.94	
S 4233	P	14	14	14		6	8	3.71	
S 4234	P	13	13	13		9	4	3.69	

* P = Pregnant; NP = Not Pregnant

Date June 30, 1972

Group 72

Appendix II

Laboratory No. 0894

Reproduction Data in Rats (Individual)

Material Aspirin

Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
A 4211	P	9	9	8		5	3	2.73	
A 4212	NP	0	0					--	
A 4213	P	12	12	8		5	3	1.47	
A 4214	P	14	14	1	1	1	1	1.60	
A 4215	P	14	14	9		8	1	2.06	
A 4216	P	9	9	1		--	--	--	
A 4217	NP	0	0					--	
A 4218	P	11	11	11		6	5	2.10	
A 4219	P	12	12	12		7	5	2.70	
A 4220	P	11	11	11		5	6	2.54	
A 4221	P		3	2		1	1	2.80	
A 4222	P	11	10	5	1	5	1	2.14	
A 4223	P	12	12	12		4	8	2.43	
A 4224	NP	0	0					--	
A 4225	P	9	9	9		3	6	2.94	
A 4226	P	14	14	14		7	7	2.50	
A 4227	P	15	14	13		8	5	2.63	
A 4228	P	12	12	10		3	7	2.03	
A 4229	P	13	13	13		9	4	3.00	
A 4230	P	16	15	3	1	2	--	1.63	
A 4231	P	14	14	14		7	7	2.72	
A 4232	P	10	10	14		6	8	--	2.10
A 4233	P	14	14	14		7	8	2.74	
A 4234	P	15	15	15		7	8		

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 77

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rats

(Individual)

Laboratory No. 0894 e

Dose 16 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 4001	P	11	11	11		4	7	3.94	
E 4002	P	16	14	14		7	7	4.12	
E 4003	P	6	6	6		4	2	4.11	
E 4004	P	11	11	10		6	4	4.04	1
E 4005	P	11	11	4		1	3	5.22	7
E 4006	P	11	11	11		5	6	4.06	
E 4007	P	11	11	11		6	5	3.62	
E 4008	P	12	12	12		7	5	4.26	
E 4009	P	13	13	13		8	5	3.60	
E 4010	P	12	12	12		7	5	3.94	
E 4011	P	11	11	9		5	4	3.62	2
E 4012	P	9	9	9		8	1	4.12	
E 4013	P	14	14	14		8	6	3.71	
E 4014	P	11	11	11		3	8	3.72	
E 4015	P	8	8	7		3	4	4.14	1
E 4016	P	14	13	13		6	7	4.37	
E 4017	P	9	6	6		--	6	3.90	
E 4018	P	11	11	11		6	5	3.65	
E 4019	P	12	12	11		6	5	3.62	1
E 4020	P	9	9	9		4	5	3.57	
E 4021	NP	0	0					--	
E 4022	P	10	10	10		5	5	3.81	
E 4023	P	11	11	11		7	4	3.68	
E 4024	P	9	8	8		3	5	3.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 78

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rats (Individual)

Laboratory No. 0894 e

Dose 75 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 4031	P	13	13	13	0	8	5	4.15	
E 4032	P	16	16	16	0	4	12	3.99	
E 4033	P	9	9	7	2	4	3	3.98	
E 4034	P	14	14	12	2	6	6	4.18	
E 4035	P	11	11	6	5	4	2	3.41	
E 4036	P	11	11	10	1	3	7	3.85	
E 4037	P	13	13	12	1	6	6	4.11	
E 4038	P	11	11	11	0	3	8	3.54	
E 4039	P	11	11	10	1	5	5	4.49	
E 4040	P	14	14	14	0	6	8	3.68	
E 4041	P	10	10	9	1	5	4	4.08	
E 4042	P	12	12	10	2	2	8	4.12	
E 4043	P	12	12	12	0	4	8	3.95	
E 4044	NP	0	0						
E 4045	P	11	11	11	0	7	4	4.07	
E 4046	P	9	9	9	0	6	3	4.02	
E 4047	P	12	12	11	1	9	2	3.55	
E 4048	P	14	14	14	0	6	8	3.90	
E 4049	P	14	14	14	0	6	8	3.84	
E 4050	P	12	12	12	0				Died Day 13
E 4051	P	11	11	11	0	7	4	3.33	
E 4052	P	11	11	11	0	6	5	3.97	
E 4053	P	15	15	11	4	4	7	3.90	
E 4054	P	9	9	8	1	3	5	3.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 79

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rats (Individual)

Laboratory No. 0894 e

Dose 350 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 4061	P	11	11	10		1	9	3.91	
E 4062	P	14	14	14		4	10	3.83	
E 4063	P	9	9	8		6	2	3.92	
E 4064	P	11	11	11		6	5	4.02	
E 4065	P	10	10	10		7	3	4.11	
E 4066	P	13	13	12		5	7	3.37	
E 4067	P	12	12	12		6	6	4.00	
E 4068	P	11	11	11		3	8	3.89	
E 4069	P	11	11	11		5	6	4.25	
E 4070	P	13	13	13		4	9	4.10	
E 4071	P	7	5	5		1	4	5.18	
E 4072	P	14	14	14		8	6	3.81	
E 4073	P	14	14	14		7	7	3.75	
E 4074	P	12	12	12		3	9	3.95	
E 4075	P	10	9	9		4	5	3.84	
E 4076	P	10	10	10		5	5	4.04	
E 4077	P	12	12	12		3	9	4.23	
E 4078	P	11	11	11		6	5	4.03	
R 4079	P	12	12	9		5	4	4.16	
E 4080	P	15	14	14		6	8	3.54	
E 4081	P	13	13	13		7	6	3.71	
E 4082	P	14	14	14		6	8	4.15	
E 4083	P	14	14	14		9	5	3.88	
E 4084	P	11	11	11		6	5	3.80	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 80

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rats (Individual)

Laboratory No. 0894e

Dose 1600 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 4091	P	12	12	12		3	9	3.68	
E 4092	P	12	12	11	1	5	6	3.88	
E 4093	P	10	10	10		4	6	4.46	
E 4094	P	10	10	10		4	6	3.82	
E 4095	P	13	11	11		5	6	4.03	
E 4096	P	13	13	13		3	10	3.95	
E 4097	P	14	14	14		5	9	3.69	
E 4098	P	15	15	13		4	9	3.40	2
E 4099	P	10	10	10		3	7	4.08	
E 4100	P	11	11	11		3	8	3.79	
E 4101	P	9	9	9		3	6	4.23	
E 4102	P	14	14	13		3	10	3.76	1
E 4103	P	13	13	13		8	5	4.35	
E 4104	P	14	14	14		3	11	3.52	
E 4105	P	12	12	10		8	2	3.83	2
E 4106	P	13	13	13		5	8	4.05	
E 4107	P	8	8	8		4	4	3.85	
E 4108	P	13	13	13		6	7	3.69	
E 4109	P	14	14	14		5	9	3.39	
E 4110	P	11	11	9		7	2	4.10	2
E 4111	P	12	12	10		5	5	3.49	2
E 4112	P	11	11	11		5	6	3.24	
E 4113	P	12	12	12		7	5	4.01	
E 4114	P	11	10	10		2	8	3.81	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

Food and Drug Research Laboratories

I N C O R P O R A T E D



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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 11, 1972

Laboratory No. 0895 e
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-15 (Gum arabic)

Examination Requested: Teratologic evaluation of FDA 71-15 in hamsters

Procedure: See Appendix I

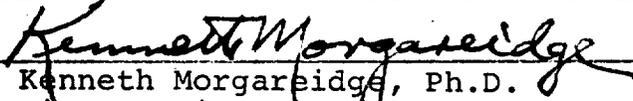
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 1600 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 71 & 72; 77 through 80

Date June 30, 1972

Material: FDA 71-15

Laboratory No. 0895 e

Table 1

Fate Summary
(Hamsters)

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
71	Sham	0	22	20	22	20
72	Aspirin*	250	21	20	21	20
77	FDA 71-15	16	21	21	20	20
78	FDA 71-15	75	23	19	23	19
79	FDA 71-15	350	21	20	21	20
80	FDA 71-15	1600	22	20	22	20

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 71 & 72; 77 through 80

Date: June 30, 1972

Material: FDA 71-15

Laboratory No.: 0895 e

Table 2

Reproduction Data
(Hamsters)

Group:	71	72	77	78	79	80
Dose (mg/kg):	Sham	Aspirin**				
Pregnancies						
Total No.	20	20	21	19	20	20
Died or Aborted (before Day 14)	0	0	2	0	0	0
To term (on Day 14)	20	20	19	19	20	20
Corpora Lutea						
Total No.						
Average/dam mated						
Live Litters						
Total No.*	20	19	18	19	20	20
Implant Sites						
Total No.	265	242	242	258	269	274
Average/dam*	13.3	12.1	12.7	13.6	13.5	13.7
Resorptions						
Total No.*	28	4	19	15	25	19
Dams with 1 or more sites resorbed	8	4	6	10	12	9
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	40.0	20.0	31.6	52.6	60.0	45.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	235	222	211	241	242	253
Average/dam*	11.8	11.1	11.1	12.7	12.1	12.7
Sex ratio (M/F)	0.71	0.73	0.49	0.54	0.67	0.62
Dead Fetuses						
Total No.*	2	16	12	2	2	2
Dams with 1 or more dead	2	3	1	2	2	2
Dams with all dead	0	1	1	0	0	0
Per cent partial dead	10.0	15.0	5.26	10.5	10.0	10.0
Per cent all dead	--	5.00	5.26	--	--	--
Average Fetus Weight, g	1.75	1.73	1.79	1.79	1.76	1.79

*Includes only those dams examined at term.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Laboratory No. 0895 e

Table 3

Material FDA 71-15

Date June 30, 1972

Summary of Skeletal Findings
(Hamsters)

Findings	Group No. Dose (mg/kg)	71 Sham	72 Aspirin**	77 16	78 75	79 350	80 1000
Live Fetuses Examined (at term)		164/20	154/19	154/19	169/19	173/20	175/20
Sternebrae							
Incomplete oss.		68/18	64/18	76/19	68/17	76/18	85/19
Scrambled							
Bipartite		13/9	34/16	6/5	30/12	15/11	19/12
Fused							
Extra				10/4		2/2	6/6
Missing		32/13	18/11	27/9	16/6	11/6	20/7
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12				1/1			
More than 13		15/9	23/13	29/12	36/16	29/14	25/13
Other							
Vertebrae							
Incomplete oss.							
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis			5/5	5/4	2/2	1/1	1/1
Tail defects							
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.				1/1			
Missing							
Extra							
Miscellaneous							
Hyoid; missing				2/2			
Hyoid; reduced			1/1	1/1			

* Numerator = Number of fetuses affected; Denominator = Number of litters affected

** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Material FDA 71-15

Laboratory No. 0895 e

Table 3-a
Summary of Soft Tissue Abnormalities
(Hamsters)

Group	Material	Dose level mg/kg	Dam	Pup	Description
77	FDA 71-15	16	E 5012	12	Generalized subcutaneous edema

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Species Hamsters

Date June 30, 1972

Laboratory No. 0895 e

Table 4

Average Body Weights*

Group	Material	Dose Level	Day				
			0	6	8	10	15**
mg/kg			g				
71	Sham	0.0	118.2	122.0	120.0	128.8	152.4 (20)
72	Aspirin***	250.0	104.6	106.3	107.5	117.2	138.0 (20)
77	FDA 71-15	16.0	118.4	121.1	124.3	133.8	154.8 (19)
78	FDA 71-15	75.0	111.2	115.2	119.0	128.3	152.7 (19)
79	FDA 71-15	350.0	116.3	117.9	121.1	130.6	154.7 (20)
80	FDA 71-15	1600.0	113.6	117.4	118.4 ^a	129.4	154.4 (20)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:

a Average based on weights of 19 dams only



Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of skeletal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 71

Appendix II

Date June 30, 1972

Material Sham

Reproduction Data in Hamsters

(Individual)

Laboratory No. 0895

Dose 0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 5211	P		17	17		6	11		1.77	
S 5212	P		14	14		5	9		1.87	
S 5213	NP								--	
S 5214	P		12	11		4	7	1	1.49	
S 5215	P		13	13		4	9		1.57	
S 5216	P		17	17		5	12		1.77	
S 5217	P		18	16		7	9	2	1.66	
S 5218	P		15	15		6	9		1.72	
S 5219	P		11	3	1	1	3	7	2.36	
S 5220	P		17	17		14	3		1.70	
S 5221	P		16	16		3	13		1.53	
S 5222	P		10	8		5	3	2	2.09	
S 5223	P		14	9		6	3	5	1.70	
S 5224	P		13	7		2	5	6	1.68	
S 5225	P		13	10		5	5	3	1.94	
S 5226	NP								--	
S 5227	P		10	10		2	8		1.87	
S 5228	P		11	11		5	6		1.78	
S 5229	P		11	9		3	6	2	1.84	
S 5230	P		9	9		4	5		1.92	
S 5231	P		10	10		5	5		1.82	
S 5232	P		14	13	1	6	7		1.62	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 72

Appendix II

Date June 30, 1972

Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 5211	P		10	10		4	6		1.90	
S 5212	P		13	13		7	6		1.63	
A 5213	P		12	12		7	5		1.75	
A 5214	P		11	11		6	5		1.94	
A 5215	P		14	14		4	10		1.62	
A 5216	P		14	14		6	8		2.02	
A 5217	P		14	14		4	10		1.83	
A 5218	P		14	0	14	--	--		--	
A 5219	P		17	17		6	11		1.82	
A 5220	NP								--	
A 5221	P		9	9		5	4		1.84	
A 5222	P		10	10		3	7		1.99	
A 5223	P		16	16		5	11		1.57	
A 5224	P		13	12		5	7	1	1.61	
A 5225	P		10	8	1	3	5	1	1.90	
A 5226	P		12	12		6	6		1.66	
A 5227	P		10	10		5	5		1.78	
A 5228	P		14	14		6	8		1.84	
A 5229	P		8	6	1	3	4	1	1.82	
A 5230	P		11	11		6	5		1.79	
A 5231	P		10	9		3	6	1	1.68	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 77

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 e

Dose 16 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 5001	P		15	15		--			
E 5002	P		17	17		11		1.96	
E 5003	P		12	10		10	2	1.78	
E 5004	P		10	7		4	3	1.90	
E 5005	P		15	15		10		1.68	
E 5006	P		15	5		10		1.96	
E 5007	P		13	13		8		1.88	
E 5008	P		15	9		4	6	1.55	
E 5009	P		14	14		11		1.55	
E 5010	P		13	13		9		1.67	
E 5011	P		15	15		10		1.59	
E 5012	P		14		12	--	2	--	Died Day 13
E 5013	P		12	12		7		1.94	
E 5014	P		8	7		6	1	1.98	
E 5015	P		11	11		7		1.80	
E 5016	P		11	11		7		1.85	
E 5017									Not assigned
E 5018	P		10	10		6		1.69	
E 5019	P		12	12		8		1.60	
E 5020	P		14	9		7	5	1.88	
E 5021	P		11	11		7		----	Aborted Day 13
E 5022	P		11	11		7		2.02	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 78 Date June 30, 1972

Appendix II

Material FDA 71-15 Laboratory No. 0895 e

Reproduction Data in Hamsters (Individual)

Dose 75 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
E 5031	P		13	11		8	4	2	1.87	
E 5032	P		15	15		6	9		1.87	
E 5033	P		13	12		2	10	1	1.91	
E 5034	P		17	14	1	--	--	2	1.67	
E 5035	P		17	17		7	10		1.92	
E 5036	NP		0						--	
E 5037	P		14	11		3	8	3	1.78	
E 5038	P		15	15		6	9		1.76	
E 5039	NP		0						--	
E 5040	P		18	17		9	8	1	1.78	
E 5041	P		11	11		4	7		1.74	
E 5042	P		18	18		8	10		1.46	
E 5043	NP		0						--	
E 5044	P		11	10		3	7	1	1.65	
E 5045										Not assigned
E 5046	P		12	11	1	5	6		1.47	
E 5047	P		10	9		3	6	1	1.51	
E 5048	P		11	11		4	7		1.85	
E 5049	NP		0						--	
E 5050	P		11	11		3	8		1.80	
E 5051	P		12	11		4	8	1	2.10	
E 5052	P		12	10		3	7	2	2.01	
E 5053	P		14	14		2	12		2.06	
E 5054	P		14	13		--	13	1	1.85	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 79

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Hamsters

(Individual)

Laboratory No. 0895 e

Dose 350 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
E 5061	P		14	14			7		2.01	
E 5062	P		17	14			10	3	1.65	
E 5063	P		18	15			8	3	1.74	
E 5064	P		14	14			12		1.83	
E 5065	P		16	14	1		9	1	1.71	
E 5066	P		13	13			8		1.77	
E 5067	P		20	20			13		1.86	
E 5068	P		13	9	1		7	3	1.75	
E 5069	P		13	10			7	3	1.89	
E 5070	P		11	10			5	1	1.68	
E 5071	P		18	17			9	1	1.72	
E 5072	P		18	14			8	4	1.49	
E 5073	P		11	11			5		1.86	
E 5074	P		11	11			5		2.08	
E 5075	P		11	9			4	2	1.55	
E 5076	P		13	12			8	1	1.57	
E 5077	P		9	8			6	1	1.56	
E 5078	NP		0						--	
E 5079	P		11	11			4		1.77	
E 5080	P		11	11			8		1.82	
E 5081	P		7	5			2	2	1.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 80

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Hamsters

(Individual)

Laboratory No. 0895 e

Dose 1600 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 5091	P		16	14		4	10	1.91	
E 5092	P		17	12	1	6	6	1.98	
E 5093	P		13	12		4	8	2.13	
E 5094	P		10	10		4	6	2.17	
E 5095	P		19	19		8	11	1.76	
E 5096	P		18	16		7	9	1.68	
E 5097	NP		0					--	
E 5098	P		15	15		7	8	1.53	
E 5099	P		17	17		6	11	1.96	
E 5100	P		18	13		6	7	2.04	
E 5101	P		12	11		3	8	1.60	
E 5102	P		17	17		9	8	1.75	
E 5103	NP		0					--	
E 5104	P		10	9		2	7	2.02	
E 5105	P		10	9		2	7	1.85	
E 5106	P		11	11		6	5	1.52	
E 5107	P		11	11		5	6	1.55	
E 5108	P		10	10		5	5	1.50	
E 5109	P		11	9		1	8	1.65	
E 5110	P		12	11	1	6	6	1.82	
E 5111	P		15	15		6	9	1.81	
E 5112	P		12	12		--	12	1.72	

* P = Pregnant; NP = Not Pregnant

RABBITS

Food and Drug Research Laboratories

INCORPORATED



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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 11, 1972

Laboratory No. 0896 e
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-15 (Gum arabic)

Examination Requested: Teratologic evaluation of FDA 71-15 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination of the data, it is tentatively concluded that:

"The administration of up to 37 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rabbits for 13 consecutive days had no clear effect on nidation or on maternal or fetal survival. The number and type of abnormalities seen in fetal soft or skeletal tissues derived from this group of does did not differ from the number occurring spontaneously in the sham-treated controls. However, in two groups of dams dosed at 173 and 800 mg/kg (body weight) respectively, maternal toxicity ensued with the loss of a majority of animals in the 800 mg/kg group (6). Death was preceded by severe bloody diarrhea, urinary incontinence, with anorexia for 48 to 72 hours terminally. At autopsy no gross pathological findings were seen other than hemorrhage in the mucosa of the small intestines. Does which survived the highest dose and bore living young to term remained outwardly normal, and the offspring were likewise normal in all respects. It is concluded that this test substance was not a teratogen in the rabbit under the test conditions employed."

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.

Vice President

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Comment: Attention is called to the fact that this is the eighth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs: each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 71 & 72; 77 through 80

Date June 30, 1972

Material: FDA 71-15

Laboratory No. 0896 e

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
71	Sham	0.0	15	14	14	13
72	6-AN*	2.5	15	13	15	13
77	FDA 71-15	8.0	15	13	13	11
78	FDA 71-15	37.0	15	13	15	13
79	FDA 71-15	173.0	15	12	12	9
80	FDA 71-15	800.0	15	14	9	8

* Positive Control: 6-amino nicotinamide dosed on Day 9

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

Group: 71 & 72; 77 through 80

Date: June 30, 1972

Material: FDA 71-15

Table 2
Reproduction Data
(Rabbits)

Laboratory No.: 0896 e

Group:	71	72	77	78	79	80
Dose (mg/kg):	Sham	6-AN**	8.0	37	173	800
Pregnancies						
Total No.	14	13	13	13	12	14
Died or Aborted (before Day 29)	1	0	2	0	3	6
To term (on Day 29)	13	13	11	13	9	8
Corpora Lutea						
Total No.	171	196	197	190	158	168
Average/dam mated	11.4	13.1	13.1	12.7	10.5	11.2
Live Litters						
Total No.*	8	11	10	11	6	5
Implant Sites						
Total No.	57	69	55	82	49	32
Average/dam*	4.38	5.31	5.00	6.31	5.44	4.00
Resorptions						
Total No.*	13	18	13	21	22	14
Dams with 1 or more sites resorbed	6	9	5	9	5	5
Dams with all sites resorbed	4	2	1	2	3	3
Per cent partial resorptions	46.2	69.2	45.5	69.2	55.6	62.5
Per cent complete resorptions	30.8	15.4	9.09	15.4	33.3	37.5
Live Fetuses						
Total No.	39	51	42	61	27	18
Average/dam*	3.00	3.92	3.82	4.69	3.00	2.25
Sex ratio (M/F)	0.50	0.55	0.68	0.69	0.93	0.64
Dead Fetuses						
Total No.*	5	0	0	0	0	0
Dams with 1 or more dead	1	--	--	--	--	--
Dams with all dead	0	--	--	--	--	--
Per cent partial dead	7.69	--	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	36.1	37.3	37.2	34.3	40.3	41.1

*Includes only those dams examined at term.
**Not applicable

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Laboratory No. 0896 e

Table 3

Material FDA 71-15

Date June 30, 1972

Summary of Skeletal Findings
(Rabbits)

Findings	Group No. Dose (mg/kg)	71 Sham	72 6-AN**	77 8.0	78 37	79 173	80 800
Live Fetuses Examined (at term)		39/8	52/11	42/10	62/11	27/6	18/5
Sternebrae							
Incomplete oss.		4/1	4/3	1/1	4/2	1/1	
Scrambled							
Bipartite			2/2		3/2		
Fused			10/7		4/4		
Extra			6/4		2/2	3/2	
Missing				1/1			
Other							
Ribs							
Incomplete oss.							
Fused/split			12/5				
Wavy							
Less than 12							
More than 13							
Other							
Vertebrae							
Incomplete oss.			2/1		1/1		
Scrambled			15/5				
Fused							
Extra ctrs. oss.							
Scoliosis			5/4				1/1
Tail defects			38/11	1/1			
Other							
Skull							
Incomplete closure							
Missing							
Craniosclerosis			7/3			1/1	
Other							
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							

* Numerator = Number of fetuses affected; Denominator = Number of litters affected

** Positive control: 6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Material FDA 71-15

Laboratory No. 0896 e

Table 3-a
Summary of Soft Tissue Abnormalities
(Rabbits)

Group	Material	Dose level mg/kg	Dam	Pup	Description
72	6-AN*	2.5	Z 6106	3	Anopia
			Z 6109	2	Anopia, club feet
			Z 6110	5	Anopia, club feet, cleft palate
			Z 6111	5	Anopia, club feet, short tail
			Z 6113	7	Anopia
			Z 6114	3	Anopia
			Z 6115	3	Anopia, club feet, short tail
			Z 6118	6	Anopia, short tail
			Z 6119	4	Anopia
			Z 6120	6	Anopia
77	FDA 71-15	8.0	E 6006	1	Medial rotation hind limbs

* 6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 71 & 72; 77 through 80

Date June 30, 1972

Species Rabbits

Table 4

Laboratory No. 0896 e

Average Body Weights*

Group	Material	Dose Level	Day				
			0	6	12	18	
mg/kg			g				
71	Sham	0.0	2.30	2.32	2.43	2.41	2.53 (13) ^e
72	6-AN**	2.5	2.41	2.45	2.49	2.53	2.63 (13)
77	FDA 71-15	8.0	2.43	2.46	2.45	2.50	2.59 (11)
78	FDA 71-15	37.0	2.38	2.38	2.42	2.46	2.54 (13)
79	FDA 71-15	173.0	2.29	2.32	2.40	2.50	2.58 (9)
80	FDA 71-15	800.0	2.01	2.08	2.09	2.11	2.30 (8)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** 6-amino nicotinamide dosed on Day 9

a Average based on weights of 10 does only



Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of



each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Date June 30, 1972

Appendix II

Group 71

Laboratory No. 0896

Reproduction Data in Rabbits (Individual)

Material Sham

Dose 0.0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 6106	P	11	4	3	0	0	3	1	45.1	
S 6107	P	13	6	6	2	2	4		25.6	
S 6108	P	9	1	1	0	0	1		32.7	
S 6109	P	8	1						----	
S 6110	P	16	8	8	4	4	4		35.0	
S 6111	P	9	1						----	
S 6112	P	12	3				3		----	
S 6113	P	9	2				2		----	
S 6114	P	12	5	3	1	1	2		38.9	
S 6115	P	14	4				4		----	
S 6116	NP	8	0						----	
S 6117	P	12	3	3	0	0	3		39.5	
S 6118	P	13	7	7	3	3	4		34.2	
S 6119	P	13	8	8	3	3	5		38.0	
S 6120	P	12	5		5	---	---		----	

Died Day 26

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 72

Appendix II

Date June 30, 1972

Material 6-AN

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896

Dose 2.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
Z 6106	P	10	4	3	1	2	1	44.6	
Z 6107	P	12	5				5	----	
Z 6108	NP	7	0					----	
Z 6109	P	11	4	2	0	2	2	33.8	
Z 6110	P	15	5	5	2	3		36.5	
Z 6111	P	16	6	4	1	3	2	31.3	
Z 6112	NP	16	0					----	
Z 6113	P	15	7	7	4	3		39.0	
Z 6114	P	15	5	4	1	3	1	38.7	
Z 6115	P	13	5	3	1	2	2	30.4	
Z 6116	P	12	3				3	----	
Z 6117	P	16	8	7	3	4	1	32.0	
Z 6118	P	15	6	6	1	5		39.0	
Z 6119	P	12	4	4	2	2		47.8	
Z 6120	P	11	7	6	2	4	1	37.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 77

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 e

Dose 8.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 6001	P	15	8				8	----	Died Day 21
E 6002	P	17	8				8	----	Died Day 18
E 6003	P	21	8	7		3	4	34.6	
E 6004	P	8	4	2		1	1	37.5	
E 6005	NP	3	0					----	
E 6006	P	19	6	6		2	4	43.7	
E 6007	P	11	5					----	
E 6008	P	12	8	4		1	3	32.4	
E 6009	P	10	4	4		3	1	41.9	
E 6010	P	13	8	8		3	5	38.5	
E 6011	P	19	4	4		1	3	43.4	
E 6012	P	13	3	3		0	3	24.9	
E 6013	P	15	3	3		2	1	36.8	
E 6014	NP	7	0					----	
E 6015	P	14	2	1		1	0	38.0	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 78

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 e

Dose 37.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
E 6016	P	22	11	9		4	5	2	33.2	
E 6017	P	12	5	3		2	1	2	42.4	
E 6018	P	15	9	7		2	5	2	27.9	
E 6019	P	9	5	4		3	1	1	24.3	
E 6020	NP	3	0						----	
E 6021	P	9	5					5	----	
E 6022	P	13	2					2	----	
E 6023	P	11	6	6		2	4	3	31.9	
E 6024	P	11	7	4		2	2	3	31.9	
E 6025	P	13	6	6		3	3		30.2	
E 6026	P	23	8	8		3	5		34.3	
E 6027	NP	14	0						----	
E 6028	P	14	8	8		3	5		34.9	
E 6029	P	9	4	1		0	1	3	47.6	
E 6030	P	12	6	5		1	4	1	38.0	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 79

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 e

Dose 173.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex	Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead				
E 6031	P	9	4	6		3	4	---	Died Day 10
E 6032	P	11	6			3		39.6	
E 6033	P	13	10				10	---	
E 6034	P	11	5	5		3		40.3	
E 6035	NP	7	0					---	
E 6036	P	8	2				2	---	Died Day 28
E 6037	P	7	2				2	---	
E 6038	NP	11	0					---	
E 6039	P	16	8	8				---	Died Day 16
E 6040	P	9	4				4	---	
E 6041	P	9	4	4		3		31.1	
E 6042	P	11	6	4		3	2	36.3	
E 6043	P	16	5	1		0	4	51.6	
E 6044	NP	6	0					---	
E 6045	P	14	7	7		2		42.8	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 80

Appendix II

Date June 30, 1972

Material FDA 71-15

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 e

Dose 800.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
E 6046	P	27	2	1		0		1	52.5	
E 6047	NP	9	0							
E 6048	P	7	1					1		
E 6049	P	8	4					4		Died Day 15
E 6050	P	11	5					5		
E 6051	P	9	3	3		0		3	43.1	
E 6052	P	16	9					9		Died Day 16
E 6053	P	11	2	2		--		--		Died Day 11
E 6054	P	9	5					5		
E 6055	P	9	7	7		4		3	32.3	
E 6056	P	8	2	2		1		1	46.1	
E 6057	P	7	3	3		--		--		Died Day 16
E 6058	P	7	1	1		--		--		Died Day 20
E 6059	P	8	7	5		2		2	31.4	
E 6060	P	22	10					10		Died Day 17

* P = Pregnant; NP = Not Pregnant